CLINICAL PRACTICE

Latent Tuberculosis Infection in the United States

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A healthy 43-year-old woman presents for a pre-employment physical examination. She is originally from Ghana and came to the United States 18 months ago. Her employer, a hospital, requires a tuberculosis test. She reports having no known exposure to tuberculosis and no cough, fevers, or weight loss. Her physical examination is unremarkable. What screening test would you recommend, and how would you decide whether treatment is needed?

THE CLINICAL PROBLEM

More than 80% of cases of tuberculosis in the United States are the result of reactivated latent infection,[1,2] and nearly all these cases could be prevented by the administration of a course of antibiotic treatment.[1] Therefore, the U.S. Public Health Service recommends screening and treatment of persons at increased risk for latent tuberculosis as the critical strategy for elimination of tuberculosis in the United States.[1,3]

There is no way to directly detect the presence of latent *Mycobacterium tuberculosis* in an individual patient. Instead, the assessment of latent infection relies on measurement of host immune responses as a surrogate for the presence of viable bacteria, an imperfect approach. Until recently, the only test for latent tuberculosis infection was the tuberculin skin test. Data from a representative survey of the U.S. population showed that 4.2% of persons who were screened with this test during 1999 and 2000 had latent tuberculosis infection.[4] Although skin testing is sensitive, its specificity for predicting reactivation tuberculosis is poor; only about 5% of immunocompetent persons with a positive test will have progression from latent infection to disease in their lifetime.[5] In addition, the antibiotic regimens that are currently recommended to prevent progression require 4 to 9 months of treatment,[1] and the rate of adherence to prolonged courses of treatment is less than 50%.[6]

Recently, two new diagnostic tests for latent tuberculosis infection have come on the market, QuantiFERON–TB Gold (QFT) (Cellestis) and the T-SPOT.TB test (Oxford Immunotec).[7] Both tests are known as interferon-γ–release assays (IGRAs) because they measure the release of interferon-γ from cells in vitro. In addition, new regimens are being used or assessed for use in treating latent tuberculosis infection. We review here the evidence in support of the use of these new tests and regimens and discuss their potential for improving the prevention of tuberculosis in the United States.

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N Engl J Med 2011;364:1441-8.

An audio version of this article is available at NEJM.org

STRATEGIES AND EVIDENCE

IDENTIFYING CANDIDATES FOR SCREENING

The risk of reactivation tuberculosis varies considerably among U.S. population subgroups. A group can have an increased risk because the prevalence of latent tuberculosis among group members is increased, as is the case among foreign-born persons; because the rate of reactivation, given latent infection, is increased, as is the case among persons infected with the human immunodeficiency virus (HIV); or because both factors are present, as is true for persons who have had recent contact with a person with infectious pulmonary tuberculosis. Table 1 shows the prevalence of latent tuberculosis infection in the United States on the basis of tuberculin skin testing. Table 2 shows the relative risk of progression from latent tuberculosis infection to disease among persons with specific conditions that increase this risk.[5]

Table 1. Prevalence of Latent Tuberculosis Infection among U.S. Residents, as Assessed by Tuberculin Skin Testing.*

Group and Study	Expected Prevalence (95% CI)
	%
Foreign-born persons	
Bennett et al.[4]	18.7 (13.5–25.2)
Close contacts of persons with infectious tuberculosis†	
Marks et al.[8]	37.1 (35.7–38.5)
Homeless persons	
Kong et al.[9]	12.8 (12.2–13.5)
Moss et al.[10]	32.4 (30.5–34.4)
Injection-drug users	
Riley et al.[11]	16.1 (12.5–22.4)
Grimes et al.[12]	27.7 (19.3–37.5)
Brassard et al.[13]	22.4 (17.7–28.5)
Salomon et al.[14]	14.0 (11.4–17.1)
Prisoners	
Lobato et al.[15]	17.0 (16.8–17.1)
U.S.-born, no other risk	
Bennett et al.[4]	1.8 (1.4–2.1)

* See the Supplementary Appendix for the definition of a positive test result. CI denotes confidence interval.
† This group was not strictly defined but is generally considered to consist of members of the household of an infected person.

Although a screening strategy that allowed identification and treatment of all cases of latent tuberculosis could prevent most cases of tuberculosis in areas with a low incidence, such as the United States, this approach would not be cost-effective. Many persons who have a positive screening result are at low risk for reactivation, and even the best screening test would identify many more false positive results than true positive results. Screening and treatment are most beneficial for those who have had contact with a person with active tuberculosis (or who have had conversion from a negative tuberculin skin test to a positive test) in the previous 2 years, those with HIV infection, persons born in high-risk countries, homeless persons, injection-drug users, and patients taking immunosuppressive medications.[22]

SELECTING A TEST

Because tuberculosis that results from reactivation of a latent infection is clinically indistinguishable from tuberculosis that results from recent exposure, reactivation tuberculosis has traditionally been defined as a disease occurring in a person who has had a positive tuberculin skin test. However, the low rate of progression among persons with a prior positive test has prompted the search for better ways to identify persons with latent tuberculosis who are at the greatest risk for progression to disease. The two commercially available IGRAs both use purified antigens from *M. tuberculosis* to stimulate peripheral-blood lymphocytes to produce interferon-γ. A single specimen of peripheral blood is drawn and incubated overnight with specific antigens for *M. tuberculosis*; interferon-γ production is then determined. The QFT test measures the amount of interferon-γ in the supernatant of a cell suspension, whereas the T-SPOT test determines the number of cells producing interferon-γ with the use of an ELISpot assay. The advantages of these tests over skin testing is that they do not require a subsequent clinical evaluation and do not have to be administered and interpreted by trained personnel on site,[23] but they do require acquisition of a blood sample and access to a laboratory that can perform the test and interpret the result (with the associated costs). Another benefit of IGRAs is the avoidance of the "booster" phenomenon (a positive result on retesting, for which the false positive rate is unclear).[24]

The incubation step selectively amplifies replication of effector memory T cells, since central

memory T cells require a longer period of in vitro incubation than effector memory T cells.[25] On the other hand, the induration produced by the tuberculin skin test contains primarily central memory T cells.[26] Whereas the tuberculin skin test may be more likely to identify persons with longstanding cellular immune responses to these antigens,[27] IGRAs are more likely to be positive in persons who have recently been infected with *M. tuberculosis*,[28] a group at particularly high risk for progression to disease (Table 2).[5]

Another potential advantage of the IGRAs is that there is no cross-reactivity with the tuberculosis vaccine — *M. bovis* bacille Calmette–Guérin (BCG). Thus, IGRAs may be particularly valuable in evaluating tuberculosis-infection status in foreign-born persons who have received BCG vaccination. The likelihood that prior vaccination will interfere with the results of the tuberculin skin test has been shown to be minimal when the interval since vaccination is longer than 10 years,[29] so the advantage is probably greatest for screening of latent tuberculosis among foreign-born children who are younger than 10 years of age. In addition, it is possible that some foreign-born persons may be more inclined to agree to treatment on the basis of a positive IGRA result as compared with a positive result on a tuberculin skin test, but data are lacking to support this view.

In an analysis of four studies conducted among household contacts of persons with active tuberculosis,[28,30-32] the pooled sensitivity of IGRAs for predicting the development of active disease within several years after exposure was 80 to 90%, the specificity 56 to 83%, the positive predictive value 4 to 8%, and the negative predictive value 99 to 100%. Two of these studies also examined the use of the tuberculin skin test to predict progression to active disease over the same period (with a positive test defined as an induration measuring 5 mm or more); the sensitivity was 90 to 100%, the specificity 29 to 39%, the positive predictive value 2.7 to 3.1%, and the negative predictive value 99 to 100%.[28,31] Thus, IGRAs appear to be somewhat more specific and less sensitive for predicting future disease than the tuberculin skin test, but the differences are modest; both types of test have low positive and high negative predictive values. Since all the studies involved persons at high risk for short-term progression to active disease, it is not clear that the findings can be generalized to persons at risk for disease over a longer period. In addition, because both IGRAs and the tuberculin skin test rely on an intact immune response, both are likely to have reduced sensitivity when used in persons with immunosuppression.[33]

Table 2. Common Risk Factors for Increased Likelihood of Progression from Latent Tuberculosis Infection to Active Disease.*

Risk Factor and Study	Relative Risk (95% CI)
	%
Advanced, untreated HIV infection	
Moss et al.[10]	9.9 (8.7–11)
Pablos-Méndez et al.[16]	9.5 (3.6–25)
Close contact with a person with infectious tuberculosis†	
Ferebee[17]	6.1 (5.5–6.8)
Radiographic evidence of old, healed tuberculosis that was not treated	
Ferebee[17]	5.2 (3.4–8.0)
Treatment with ≥15 mg of prednisone per day‡	
Jick et al.[18]	2.8 (1.7–4.6)
Chronic renal failure	
Pablos-Méndez et al.[16]	2.4 (2.1–2.8)
Treatment with TNF-α inhibitor	
Askling et al.[19]	2.0 (1.1–3.5)
Poorly controlled diabetes	
Pablos-Méndez et al.[16]	1.7 (1.5–2.2)
Weight ≥10% below normal	
Palmer et al.[20]	1.6 (1.1–2.2)
Smoking	
Bates et al.[21]	1.5 (1.1–2.2)

* Relative risk was calculated as described in Horsburgh.[5] CI denotes confidence interval, HIV human immunodeficiency virus, and TNF tumor necrosis factor.
† Relative risk was calculated for the first 3 years after exposure.
‡ The drug was taken for 2 weeks or more.

CHOOSING TREATMENT

Given the high risks of drug resistance and of treatment failure if patients with unsuspected active tuberculosis are treated with a single-drug regimen, careful evaluation for active disease must precede initiation of treatment for latent infection. Decisions about whether to treat latent tuberculosis should take into account the individual patient's risk for the development of active tuberculosis and the risks of therapy. The lifetime risk of the development of active disease in an im-

munocompetent person with latent tuberculosis depends on demographic and clinical characteristics and ranges from 1 to 13%.[5]

Two regimens are now jointly recommended for the treatment of latent tuberculosis by the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America (ATS–CDC–IDSA) (with two different durations of isoniazid therapy considered to be one regimen) (Table 3).[1] Randomized trials have shown that treatment is highly effective, with approximately 90% protection provided by completion of a 9-month course of isoniazid and 60 to 80% protection provided by completion of a 6-month course.[1] The second recommended regimen — administration of rifampin for 4 months — has not been directly evaluated, but in one randomized trial in which patients received rifampin for 3 months, 60% protection was conferred.[37] A clinical trial of a 4-month regimen of rifampin is ongoing (ClinicalTrials.gov number, NCT00170209). A 3-month regimen of isoniazid and rifampin, although not recommended by the ATS–CDC–IDSA, provided 60% protection in a trial involving persons infected with HIV.[38] In a meta-analysis of four small randomized trials, this regimen appeared to provide similar protection for persons not infected with HIV.[36] Another regimen, consisting of both rifapentine and isoniazid administered once a week for 3 months, had a low rate of serious hepatotoxicity (1%; 95% confidence interval, 0.1 to 3.5)[35]; in an ongoing trial, the effects of this regimen are being directly compared with those of a 9-month course of isoniazid (NCT00023452).

Hepatotoxicity is a serious potential side effect of both isoniazid and rifamycins (Table 3). This risk is increased among persons with chronic liver disease and among those who consume substantial amounts of alcohol or other hepatotoxins. Isoniazid may also cause peripheral neuropathy, although its development can be prevented with the coadministration of pyridoxine. Because rifampin interferes with the metabolism of many drugs, it may not be a good choice for some patients, particularly women taking oral contraceptives or persons with HIV infection who are taking protease inhibitors or non-nucleoside reverse-transcriptase inhibitors. Rifabutin, a rifamycin antibiotic that has fewer pharmacologic interactions with antiretroviral agents than rifampin, has been used in combination with isoniazid for the treatment of latent tuberculosis infection,[39] but its efficacy in preventing progression from latent infection to active disease has not been studied.

An important determinant of the effectiveness of the treatment of latent tuberculosis infection is adherence to the regimen. Although side effects contribute to low completion rates, they account for a small fraction of the patients who do not complete treatment. The likelihood of completion is better with shorter regimens, with reported completion rates of 45 to 60% with 9 months of daily isoniazid, 55 to 57% with 6 months of daily isoniazid, 69 to 78% with 4 months of daily rifampin, and 75% with 3 months of daily isoniazid and rifampin.[35,40,41]

MONITORING TREATMENT

Data from prospective studies are lacking to provide guidance with respect to optimal strategies for monitoring treatment. Most guidelines recommend initial screening with liver-enzyme profiles for patients with underlying liver disease or HIV infection, women who are pregnant or post partum, and patients who consume substantial amounts of alcohol or medications with hepatotoxic potential. Follow-up with monthly assays for serum aminotransferase levels is recommended only in patients whose baseline levels are elevated. Monthly clinical monitoring for signs and symptoms of toxicity is recommended. For patients with symptoms who have aminotransferase levels that are more than three times the upper limit of the normal range (or those without symptoms who have levels that are more than five times the upper limit of the normal range), treatment should be discontinued.[1]

GUIDELINES FROM PROFESSIONAL SOCIETIES

Screening guidelines for latent tuberculosis infection in the United States are compared with those from Canada and the United Kingdom in Table 4. The recommendations vary, but all endorse the use of IGRAs in some circumstances, with U.S. guidelines advising that IGRAs can be used interchangeably with the tuberculin skin test in most circumstances. The guidelines are likely to evolve as more data on IGRAs become available. The treatment regimens recommended in the guidelines from Canada and the United King-

Table 3. Drug Regimens for the Treatment of Latent Tuberculosis Infection.

Drug	Adult Dosage	Pediatric Dosage	Side Effects		Discontinuation Due to Adverse Event in Clinical Trials (95% CI)
			Risk of Hepatotoxicity, Grade 3 or 4 (95% CI)	Less Common Side Effects	
			%		%
Isoniazid	300 mg daily or 900 mg twice weekly for 9 mo or 6 mo*	10–20 mg/kg body weight daily or 20–40 mg/kg twice weekly for 9 mo or 6 mo†	3.8 (2.3–6.1)†	Rash and peripheral neuropathy	3.7 (2.3–6.1)†
Rifampin	600 mg daily for 4 mo	10–20 mg/kg for 4 mo	0.7 (0.2–2.1)	Leukopenia, thrombocytopenia, and drug interactions with birth-control pills, methadone, and some antiretroviral agents	2.1 (1.1–4.0)†
Rifampin plus isoniazid‡	600 mg of rifampin plus 300 mg of isoniazid daily for 3 mo	10–20 mg of rifampin/kg plus 10–20 mg/kg daily for 3 mo	Not specified§	For rifampin leukopenia, thrombocytopenia, and drug interactions with birth-control pills, methadone, and some antiretroviral agents; for isoniazid, rash and peripheral neuropathy	4.9 (3.7–6.5)†§

* A 9-month course of isoniazid is preferred, but for patients who cannot complete a 9-month course, a 6-month course still provides some protection and is an alternative recommendation.
† Data are from Menzies et al.[34]
‡ The regimens for rifampin plus isoniazid were not included in the 2000 joint guidelines from the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America.[1] Although the guidelines for its use are less well established than those for the other regimens listed, a meta-analysis suggests that its safety and efficacy are similar to those of isoniazid alone.[35]
§ Data are from Ena and Valls.[36]

Table 4. Screening Guidelines from the United States, Canada, and the United Kingdom for Selected Groups at Risk for Latent Tuberculosis (TB) Infection.*

Risk Group	U.S. Guideline	Canadian Guideline	U.K. Guideline
Close contacts of persons with infectious TB	TST or IGRA, but not both	TST, with IGRA to confirm positive TST	TST, with IGRA to confirm positive TST
Persons who may not return for TST reading because of circumstances (e.g., homelessness or injection-drug use) or logistic difficulties	IGRA preferred	No specific recommendation	IGRA preferred
Immunosuppressed persons (e.g., those infected with HIV or receiving treatment with prednisone or TNF-α inhibitor)	TST or IGRA; use both if first is negative and suspicion is high	TST, followed by IGRA if TST is negative	TST or IGRA
Foreign-born persons	Screening only for those who have immigrated in past 5 yr; use TST or IGRA, but not both	Screening only for those <15 yr old who have immigrated in past 2 yr; use TST, with IGRA to confirm positive TST	Screening for new immigrants only; use TST with IGRA to confirm positive TST for those 5-15 yr of age and IGRA for those 16-35 yr of age
BCG vaccine recipients (if they belong to another risk group)	IGRA preferred	No specific recommendation	TST or IGRA
Health care workers (screening program)	TST or IGRA, but not both	TST preferred	TST or IGRA, depending on specific circumstances
Children <5 yr old	TST preferred	No specific recommendation	TST preferred
Other risk groups	TST or IGRA, but not both	TST, with IGRA to confirm positive TST	TST, with IGRA to confirm positive TST

* The sources for the U.S., Canadian, and U.K. guidelines, respectively, are as follows: the Centers for Disease Control and Prevention,[42] the Public Health Agency of Canada[43,44], and the U.K. National Institute for Health and Clinical Excellence.[45] BCG denotes bacille Calmette–Guérin, HIV human immunodeficiency virus, IGRA interferon-γ release assay, and TST tuberculin skin test.

dom are similar to those supported in the U.S. guidelines, although the guidelines from the United Kingdom state that a 3-month course of isoniazid and rifampin therapy is a reasonable alternative to the use of isoniazid alone.[1,42-45]

AREAS OF UNCERTAINTY

The fact that differing conclusions were reached on the optimal use of IGRAs by expert panels in the United States, Canada, and the United Kingdom underscores the need for more research to guide screening strategies, especially for persons with a low risk of progression from latent tuberculosis infection to clinical disease and for those at low risk for infection but at high risk for progression, should they become infected (e.g., health care workers). Although cutoff points for a positive tuberculin skin test have been defined for groups at different levels of risk (see the Supplementary Appendix, available with the full text of this article at NEJM.org), there is uncertainty regarding the value of adjusting IGRA cutoff points for groups with different levels of risk. Moreover, for the tuberculin skin test, conversion is defined as an increase in induration of 10 mm or more, but there is no definition of conversion for IGRAs, and variation in the interpretation of cutoff points can result in a falsely positive finding of conversion; this has led to difficulties when IGRAs are used in screening programs for health care workers.[46]

Research is also needed to facilitate identification of those patients with latent infection who are at highest risk for progression to active disease. It is conceivable that immunologic or genetic tests will be able to identify such patients before reactivation takes place; such testing is unlikely to be feasible if reactivation is determined by unpredictable events (e.g., acquired immune suppression).

Clinical trials are needed to determine the efficacy of new antimycobacterial agents in the treatment of persons with latent tuberculosis infection, including those who have been exposed to drug-resistant disease. Most current antimycobacterial agents have a limited ability to kill nonreplicating bacteria that may be important in maintaining latency. Newer investigational compounds, such as TMC207, which appear to kill dormant or semidormant *M. tuberculosis* cells, might allow for further shortening of the dura-

tion of treatment for latent tuberculosis infection.[47,48] The optimal strategy for monitoring patients who are receiving treatment for latent tuberculosis remains uncertain.

RECOMMENDATIONS

Our recommendations for screening are a blend of those in the published guidelines: screening is recommended only for population subgroups with a high prevalence of latent tuberculosis infection or those with a high likelihood of progression from latent tuberculosis infection to active disease (Tables 1 and 2). Although data informing the optimal approach to screening in various subgroups are limited, we prefer the use of IGRAs when the prevalence of recent infection is likely to be high: these populations include close contacts of patients with active tuberculosis, recently arrived foreign-born persons, drug users, incarcerated persons, and homeless persons. IGRAs are also of value for screening persons who have received the BCG vaccine. For populations in which the prevalence is low or infection is likely to have been remote, we prefer the tuberculin skin test because IGRAs have either not been well studied (e.g., among smokers or persons with diabetes mellitus) or have performed poorly (e.g., among health care workers). Screening with either test is not recommended in persons at low risk, since such persons are much more likely to have false positive than true positive results. Either test would be appropriate for screening the patient described in the vignette.

All patients with evidence of latent tuberculosis should undergo clinical evaluation and chest radiography for active tuberculosis before being offered treatment for latent tuberculosis. Although current U.S. guidelines endorse 6 or (preferably) 9 months of treatment with isoniazid or 4 months of treatment with rifampin, we prefer the 4-month regimen with rifampin because completion rates are higher and side effects are fewer than with the other regimens. The results of liver-function tests should be evaluated before treatment is initiated. If the results are normal, repeat tests of liver function are not routinely recommended, but it is prudent to monitor patients monthly for symptoms or signs suggesting drug toxicity and for adherence to therapy. Even when 3- or 4-month regimens are prescribed, nearly a quarter of patients do not complete treatment. Patients should understand that the protection conferred by an incomplete course of treatment is likely to be substantially compromised as compared with the protection provided when the course of treatment is completed.

Dr. Rubin reports serving on an unpaid scientific advisory board for the Global Alliance for TB Drug Development and receiving consulting fees and travel reimbursement from Novartis; and Dr. Horsburgh, receiving consulting fees from Otsuka Pharmaceutical. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Web Supplementary Table. Criteria for a positive tuberculin skin test (TST) reaction in various clinical settings

Induration size	Risk group
5mm or greater	HIV-infected persons
	Recent contacts of active TB cases
	CXR evidence of old TB
	Immunocompromising medications or conditions^
10 mm or greater	Recent immigrants (within ≤5 years) from TB endemic areas
	Injection drug users
	Employees and residents in high risk settings¶
	TB laboratory personnel
	Medical conditions that increase the risk of TB*
	Children (<4 years old) exposed to adults at high risk for TB but not known to be TB cases
15 mm or greater	All others

Adapted from CDC/ATS/IDSA guidelines[1]
^e.g., TNF-alpha inhibitor or corticosteroid therapy
¶Prisons, jails, nursing homes, health care facilities, homeless shelters
*Silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, lung cancer, head and neck cancer, >10% weight loss, gastrectomy, jejunoileal bypass